

What is claimed:

1. A method for the treatment of a mammal, suffering from or susceptible to emesis, comprising administration of an effective amount of a tachykinin antagonist which is an NK<sub>1</sub> antagonist in combination with one or more other therapeutic agents selected from systemic anti-inflammatory corticosteroids or 5HT<sub>3</sub> antagonists.

① 2. A method according to claim 1 wherein the systemic anti-inflammatory corticosteroid is methyl prednisolone or dexamethasone.

3. A method according to claim 1 wherein the 5HT<sub>3</sub> antagonist is ondansetron, granisetron or metoclopramide.

4. A method according to claim 1 wherein said emesis is induced by cancer chemotherapeutic agents, radiation sickness, radiation therapy, poisons, toxins, pregnancy, vestibular disorders, post-operative sickness, gastrointestinal obstruction, reduced gastrointestinal motility, visceral pain, migraine, increased intracranial pressure, decreased intracranial pressure, or opioid analgesics.

5. A method according to claim 4 wherein said emesis is induced by a cancer chemotherapeutic agent.

6. A method according to claim 5 wherein said cancer chemotherapeutic agent is selected from cyclophosphamide, carmustine, lomustine, chloroambucil, dactinomycin, doxorubicin, mitomycin-C, bleomycin, cytarabine, methotrexate, 5-fluorouracil, etoposide, vinblastine, vincristine, cisplatin,

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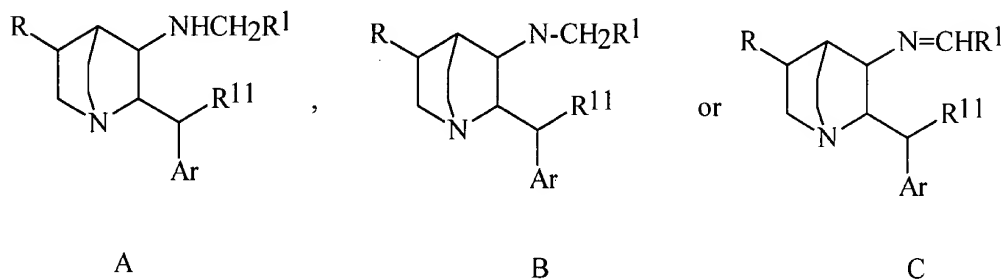
dacarbazine, procarbazine, hydroxyurea, and combinations thereof.

7. A method according to claim 6 wherein said emesis is induced by cisplatin.

8. A method according to claim 6 wherein said emesis is induced by cyclophosphamide.

9. A method according to claim 1 wherein said emesis is induced by morphine, ipecacuanha or copper sulfate.

10. A method according to claim 1 wherein the NK<sub>1</sub> antagonist is a compound of formula:



wherein

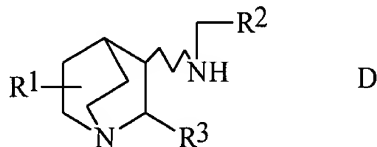
Ar is thienyl, phenyl, fluorophenyl, chlorophenyl or bromophenyl;

R is hydrogen or alkyl having one to four carbon atoms;

R<sup>1</sup> is cycloalkyl having from five to seven carbon atoms, norbornyl, pyrrolyl, 2,3-dihydrobenzofuranyl, thienyl, alkoxythienyl having from one to three carbon atoms in the alkoxy moiety, pyridyl, hydroxypyridyl, quinolinyl, indolyl, naphthyl, alkoxynaphthyl having from one to three carbon atoms

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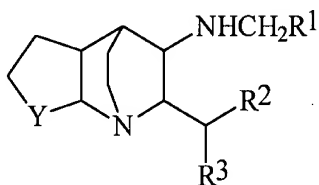
in the alkoxy moiety, biphenyl 2,3-methylenedioxyphenyl, or phenyl optionally substituted with up to two substituents selected from cyano, nitro, amino, N-monoalkylamino having from one to three carbon atoms in the alkyl moiety, fluorine, chlorine, bromine, trifluoromethyl, alkyl having from one to three carbons, alkoxy having from one to three carbon atoms, allyloxy, hydroxy, carboxy, alkoxycarbonylbenzyloxy having from one to three carbon atoms in the alkoxy moiety, carboxamido or N,N-dialkylcarboxamido having from one to three carbon atoms in the alkyl moiety; and R<sup>11</sup> is branched chain alkyl having from three to four carbon atoms, branched chain alkenyl having from five to six carbon atoms, cycloalkyl having from five to seven carbon atoms, furyl thienyl, pyridyl, indolyl, biphenyl, or phenyl optionally substituted with up to two substituents selected from fluorine, chlorine, bromine, trifluoromethyl, alkyl having from one to three carbon atoms, alkoxy having from one to three carbon atoms, carboxy, alkoxycarbonyl having from one to three carbon atoms in the alkoxy moiety or benzyloxycarbonyl, with the proviso that said R<sup>11</sup> is always other than unsubstituted phenyl, fluorophenyl, chlorophenyl, bromophenyl or alkylphenyl when said R<sup>1</sup> is unsubstituted phenyl, pyrrolyl or thienyl and Ar is other than thienyl;



wherein R<sup>1</sup> is hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl;

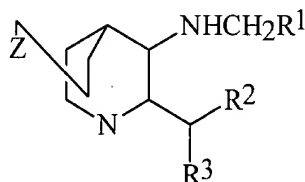
R<sup>2</sup> is phenyl, pyridyl, thienyl or furyl, and R<sup>2</sup> may optionally be substituted with from one to three substituents independently selected from (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, chloro, fluoro, bromo, iodo and trifluoromethyl;

$R^3$  is phenyl, naphthyl, pyridyl, thienyl or furyl, and  $R^3$  may optionally be substituted with one to three substituents independently selected from  $(C_1-C_4)$ alkyl,  $(C_1-C_4)$ alkoxy, chloro, fluoro, bromo, iodo and trifluoromethyl;

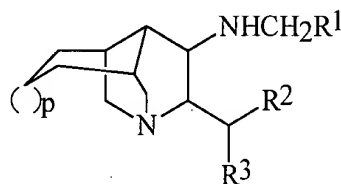


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or



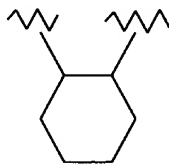
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wherein

Y is  $(CH_2)_m$  wherein m is an integer from one to three, or Y is a group of the formula



P is an integer from zero to one;

Z is oxygen, sulfur, amino, N- $(C_1-C_3)$ alkylamino or  $-(CH_2)_n-$  and n is zero, one or two;

Ar is thienyl, phenyl, fluorophenyl, chlorophenyl or bromophenyl;  $R^1$  is cycloalkyl having from five to seven carbon

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atoms, pyrrolyl, thienyl, pyridyl, phenyl or substituted phenyl, wherein said substituted phenyl is substituted with one to three substituents selected from fluorine, chlorine, bromine, trifluoromethyl, alkyl having from one to three carbon atoms, alkoxy having from one to three carbon atoms, carboxy, alkoxycarbonyl having from one to three carbons in the alkoxy moiety and benzyloxycarbonyl; and

R<sup>2</sup> is furyl, thienyl, pyridyl, indolyl, biphenyl, phenyl or substituted phenyl, wherein said substituted phenyl is substituted with one or two substituents selected from fluorine, chlorine, bromine, trifluoromethyl, alkyl having from one to three carbon atoms, alkoxy having from one to three carbon atoms, carboxy, alkoxycarbonyl having from one to three carbon atoms in the alkoxy moiety and benzyloxycarbonyl; or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition for the treatment or prevention of emesis comprising a 5HT<sub>3</sub> receptor-antagonist, an NK-1 receptor antagonist and a pharmaceutically acceptable carrier.

12. The pharmaceutical composition of claim 11, wherein the 5HT<sub>3</sub> receptor antagonist is selected from the group consisting of ondansetron and granisetron.

13. The pharmaceutical composition of claim 11, wherein the NK-1 receptor antagonist is selected from the group consisting of cis-3-(2-methoxybenzyl)amino-2-phenylpiperidine, cis-3-[(2-methoxyphenyl)methylamino]-2-benzhydryl-quinuclidine, cis-3-[(2-methoxybenzyl)amino]-2-diphenylmethyl-1-azabicyclo[2.2.2]octane and (exo,exo)-2-diphenylmethyl)-N-[5-

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fluoro-2-methoxyphenyl)methyl]-1-azabicyclo[2.2.1] heptan-3-amine.

14. A method of treating or preventing emesis in a mammal, comprising administering to said mammal an anti-emetic effective amount of a pharmaceutical composition comprising a 5HT<sub>3</sub> receptor antagonist, an NK-1 receptor antagonist and a pharmaceutically acceptable carrier.

15. The method of claim 14, wherein the 5HT<sub>3</sub> receptor antagonist is selected from the group consisting of ondansetron and granisetron.

16. A method of treating or preventing emesis in a mammal, comprising administering to said mammal a 5HT<sub>3</sub> receptor antagonist and an NK-1 receptor antagonist in amounts that render the combination of such two active agents effective in the treatment or prevention of such disorder.

17. The method of claim 14 or 15, wherein the NK-1 receptor antagonist is selected from the group consisting of cis-3-(2-methoxybenzyl)amino-2-phenylpiperidine, cis-3-[(2-methoxyphenyl)methylamino]-2-benzhydryl-quinuclidine, cis-3-[(2-methoxybenzyl)amino]-2-diphenylmethyl-1-azabicyclo[2.2.2]octane and (exo,exo)-2-diphenylmethyl)-N-[5-fluoro-2-methoxyphenyl)methyl]-1-azabicyclo[2.2.1] heptan-3-amine.

18. The method of claim 16, wherein the NK-1 receptor antagonist is selected from the group consisting of cis-3-(2-methoxybenzyl)amino-2-phenylpiperidine, cis-3-[(2-methoxyphenyl)methylamino]-2-benzhydryl-quinuclidine, cis-3-[(2-methoxybenzyl)amino]-2-diphenylmethyl-1-azabicyclo[2.2.2]octane

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and (exo,exo)-2-diphenylmethyl)-N-[5-fluoro-2-methoxyphenyl)methyl]-1-azabicyclo[2.2.1] heptan-3-amine.

19. The method of claim 16, wherein the 5HT<sub>3</sub> receptor antagonist is selected from the group consisting of ondansetron and granisetron.

20. The method of claim 14, wherein the combination of the 5HT<sub>3</sub> receptor antagonist and the NK-1 receptor is used to treat or prevent ondansetron-resistant emesis.

21. The method of claim 16, wherein the combination of the 5HT<sub>3</sub> receptor antagonist and the NK-1 receptor is used to treat or prevent ondansetron-resistant emesis.

22. The method according to claim 14, wherein the NK-1 receptor antagonist is administered in an amount from about 0.1 to 400 mg per kg body weight of the subject being treated per day and the 5HT<sub>3</sub> receptor antagonist is administered in an effective amount.

23. The method according to claim 14, wherein the composition is administered at a dose of 3 mg/kg.

24. The method according to claim 14, wherein the composition is administered at a dose of 5 mg/kg.

25. The method according to claim 14, wherein the 5HT<sub>3</sub> receptor antagonist and the NK-1 receptor antagonist are administered separately according to a dosed regimen that renders the combination of the separately administered active agents effective in the treatment or prevention of emesis.

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